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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,883	01/22/2002	Carlota Vinals Y De Bassols	BC45224	6044

20462 7590 01/24/2005

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER

YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/914,883

Applicant(s)Y DE BASSOLS, CARLOTA
VINALS**Examiner**

Christopher H Yaen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 October 2004.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-45 is/are pending in the application.
4a) Of the above claim(s) 20 and 24-45 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 17-19 and 21-23 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1/22/02, 3/15/04.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Exhibits A and B.

DETAILED ACTION

Re: Vinals-Bassols
Priority Date: 28 February 2000

Election/Restrictions

1. Applicant's election of group I (claims 17-19 and 21-23, specifically drawn to SEQ ID No: 2) in the reply filed on 10/25/2004 is acknowledged. Applicant argues that the separation of the inventions into the different groups is discretionary, but failed to provide any substantial arguments as to why the inventions should be regroup into a single invention. Therefore, as indicated in the prior office action (mailed 9/20/2004) the special technical feature linking the invention does not contribute over the prior art and therefore unity of invention is still lacking. Moreover, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Claims 17-45 are pending, claims 20, and 24-45 are withdrawn as being drawn to non-elected invention(s).
3. Claims 17-19 and 21-23 are examined on the merits.

Information Disclosure Statement

4. The Information Disclosure Statements filed 1/11/2002 and 3/15/2004 are acknowledged and considered. Signed copies of the IDSs are attached hereto.

Claim Objections

5. Claims 17-19 are objected to because of the following informalities: claims recite terms that are drawn to non-elected inventions (i.e. claims recite SEQ ID No: 4).
Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 18-19 and 21-23 are also rejected because these claims depend on base claim 17.

Specifically, claim 17 recites the phrase "which can include an adjuvant or a suitable carrier coupled to the polypeptide", it is unclear as to whether these elements (i.e. adjuvants or carriers) are part of the invention. Moreover, it is unclear if these elements are required for the function of eliciting an immune response. Appropriate correction or clarification is required.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 17-18 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set forth an amino acid sequence that consists of or comprises SEQ ID No: 2 and therefore the written description in this case is not commensurate in scope to the claims that read on variants, fragments, immunogenic fragments, or homologues of SEQ ID No: 2.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlag, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of variant proteins encoded by allelic variant genes defined. With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the variants, fragments, and or homologues encompassed and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai*

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Pharmaceutical Co. Lts., 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

The specification teaches (pages 3-4) that variants, fragments, immunogenic fragments and or homologues can encompass a genus of peptide sequences with the stated biological properties. However, the written description only reasonably conveys the peptide CASB616 (SEQ ID NO: 2). The instant disclosure of a single species of a peptide fails to adequately describe the scope of the claimed genus (any peptide sequence that is a variant, homologue or fragment), which encompasses a substantial variety of peptide sequences. A description of a genus of peptide variants, fragments, or homologues may be achieved by means of a recitation of a representative number of such sequences, defined by structure, falling within the scope of the genus. However, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of peptides sequences that would distinguish the claimed peptide sequences from other sequences that do not have the claimed biological properties. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one specific peptide is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are

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clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only an isolated CASB616 polypeptide having an amino acid sequence of SEQ ID NO. 2 meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 101

8. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility.

The current claims are drawn to an isolated polypeptide comprising a member selected from (a) an amino acid sequence that is at least 90% identical to SEQ ID No: 2; (b) an immunogenic fragment that is at least 90% identical to that of SEQ ID No: 2; and (c) an immunogenic fragment that is at least 90% identical to SEQ ID No: 2 that has no more than 5 single amino acid substitutions, deletions, or additions. Subsequent

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claims limit or narrow the percent identity to SEQ ID No: 2 or limit the number of single amino acid substitutions, deletions, or additions.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The specification cites, as utilities for the CASB616 protein (SEQ ID No: 2), that the polypeptides are useful as treatments for cancer or autoimmune disease (see page 1, line 5) and in the diagnosis of tumor cells (see page 2, line 24). These utilities are credible.

Upon identification of a credible utility, the next issue is whether there are any well established utilities for the CASB616 protein (SEQ ID No: 2). A review of the specification and of the prior art finds no well established utilities for the use of the unknown protein termed CASB616 (SEQ ID No: 2), whose enzymatic or other biological function and whose cellular roles are entirely unknown and undisclosed in the specification.

The next inquiry is whether there are substantial or specific utilities for the CASB616 protein (SEQ ID No: 2) which are identified in either the specification or in the prior art.

Substantial Utility

Here, the evidence in the specification provides that the nucleic acid (mRNA) that encodes the polypeptide of CASB616 is over-expressed in malignant colon cells (see

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page 31). However, the specification fails to show that this over-expression in mRNA levels is directly correlative to over-expression in protein levels, nor has the specification taught that over-expression of the mRNA is indicative of any specific malignancies or involvement in autoimmune diseases. Moreover, one of skill in the art cannot extrapolate from the findings provided in the specification (such as on page 31), although drawn to the mRNA analysis, how the instantly claimed protein can be used in the detection of cancer or in autoimmune diseases, based only on the finding of mRNA over-expression in colon tissue samples. Even if there was a differential expression between normal and malignant colon tissue samples, the specification has not taught one of skill in the art that the claimed CASB616 protein is in fact expressed or over-expressed.

There is an abundance of art that teaches that the regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen, M et al, 1995, Pediatric Res, 37 (6): 681-686). Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine

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decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be over-expressed in CHO cells following exposure to radiation, without any concomitant over-expression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988, Vol. 3, pp. 471-475) teach that the retinoblastoma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus in the instant case, one of skill in the art would not be able to predict if the CASB616 protein (SEQ ID No:2) or polypeptides that are 90-95% identical to SEQ ID No: 2 is in fact translated into a polypeptide expression product, or even if translated, whether they are over-expressed.

This situation is also analogous to example 4 of the Utility Guidelines, where a protein was disclosed by reference to a SEQ ID number and methods of making the

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protein, but fails to disclose any chemical, physical, or biological properties for the protein other than the sequence, was found to lack utility. In the current case, the CASB616 protein (SEQ ID No: 2), lacks any substantial utility whatsoever and therefore any variant, fragment or homologue thereof would also lack a substantial utility. The specification does not even show that the protein is endogenously expressed in tissues as a protein, (the specification however does provide prophetic embodiments of expressing the protein recombinantly, see pages 34-35). So this case is similar to the uncharacterized protein of Example 4, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for CASB616. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for this CASB616 protein (SEQ ID No: 2) or any variant, fragment or homologue thereof. The protein, itself, has not been associated with any disease, any condition, or any other specific feature. There is no association of the protein with cancer or with any other disease, such as autoimmune disorders/diseases. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be

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diagnosed". Here, the over-expression of the mRNA in cancerous colon tissue gives no specific utility for the protein or any variant, fragment or homologue thereof because the protein or any variant, fragment or homologue thereof has not been shown to be useful diagnostically, and it does not provide any evidence indicating a possible therapeutic use and simply represents a protein which may be expressed in a tissue. Until some function or some activity of the protein is identified, the protein or any variant, fragment or homologue thereof has no use. Therefore, there is no specific utility for the CASB616 protein or any variant, fragment or homologue thereof until a specific biological function or activity is identified.

With regard to the utility analysis, the current situation directly tracks that of examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility.

Given the teachings of unpredictability associated with protein expression and the lack of endogenous protein expression data of CASB616 in the specification, one of skill in the art cannot with any certainty correlate the teachings of the instant specification with any specific disease treatment or diagnosis, such as cancer or autoimmune diseases. Because the specification has only provided an expression profile of the CASB616 mRNA and has not taught how the instantly claimed protein functions, what its cellular role is, and what specific or substantial use the claimed polypeptide would have, utility is lacking. As such, the specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide and fragments thereof. Because the claimed invention is not

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supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claims 17-19 and 21-23 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Pawson *et al* (WO 97/14966-A1). Claims are drawn to a isolated polypeptide comprising a member selected from (a) an amino acid sequence that is at least 90% identical to SEQ ID No: 2; (b) an immunogenic fragment that is at least 90% identical to that of SEQ ID No: 2; and (c) an immunogenic fragment that is at least 90% identical to SEQ ID No: 2 that has no more than 5 single amino acid substitutions, deletions, or additions. Claim 18 limits the percent identity of SEQ ID No: 2 to 95%, claim 19 limits the polypeptide as having the sequence of SEQ ID No: 2, claims 21-22 limit the claims to having no more than two single or a one single amino acid substitution, deletion, or either, respectively, and claim 23 limits the immunogenic

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fragment to that which matches the aligned sequence. For the purposes of this rejection, the term “has” in claim 19 is interpreted as being open and is read to the extent that the term means “containing” a sequence of SEQ ID No: 2. Furthermore, because of the indefiniteness of claim 17, which recites “which can include an adjuvant or a suitable carrier”, for the purposes of this rejection, the claim can be interpreted as either having or NOT having adjuvants or carriers.

Pawson *et al* teach a sequence (also known as SEQ ID No: 2, herein SEQ ID No: 2*) that has at least 98.9% identity to that of SEQ ID No: 2 (see attached Exhibit A). Pawson *et al* also teach fragments of SEQ ID No: 2' (see page 5, lines 12-18). Because the office does not have the ability to determine if the fragments taught by Pawson *et al* are indeed immunogenic, in the absence of evidence to the contrary, the fragments are immunogenic fragments. Further, because the sequence taught by Pawson *et al* is 98.9% identical to SEQ ID No: 2 it necessarily fulfills the limitation of at least 95% identical to that of SEQ ID No: 2. Moreover, Pawson *et al* also disclose fragments that are at least 20 contiguous amino acids from SEQ ID No: 2* (see page 5, lines 12-18) and therefore falls within the scope of both “no more than two” or “no more than one” single amino acid substitution, deletion, or addition, because no amino acid is either substituted, deleted or added to the fragment. And finally, because SEQ ID No: 2 is 98.9% identical to that of SEQ ID No: 2' and because fragments have been disclosed by Pawson *et al*, it would also “match the aligned sequences” as claimed.

If claim 17 is interpreted as having carriers, Pawson *et al* teaches that pharmaceutical carriers can be included in the invention (see page 5, lines 12-18).

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 102(e) as being anticipated by Pawson *et al* (US Patent 6,218,356). Claims are drawn to a isolated polypeptide comprising a member selected from (a) an amino acid sequence that is at least 90% identical to SEQ ID No: 2; (b) an immunogenic fragment that is at least 90% identical to that of SEQ ID No: 2; and (c) an immunogenic fragment that is at least 90% identical to SEQ ID No: 2 that has no more than 5 single amino acid substitutions, deletions, or additions. Claim 18 limits the percent identity of SEQ ID No: 2 to 95%, claim 19 limits the polypeptide as having the sequence of SEQ ID No: 2, claims 21-22 limit the claims to having no more than two single or a one single amino acid substitution, deletion, or either, respectively, and claim 23 limits the immunogenic fragment to that which matches the aligned sequence. For the purposes of this rejection, the term “has” in claim 19 is interpreted as being open and is read to the extent that the term means “containing” a sequence of SEQ ID No: 2. Furthermore, because of the indefiniteness of claim 17, which recites “which can include an adjuvant

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or a suitable carrier", for the purposes of this rejection, the claim can be interpreted as either having or NOT having adjuvants or carriers.

Pawson *et al* teach a sequence (also known as SEQ ID No: 2, herein SEQ ID No: 2*) that has at least 98.9% identity to that of SEQ ID No: 2 (see attached Exhibit B). Pawson *et al* also teach fragments of SEQ ID No: 2* (see col. 7, lines 41-52). Because the office does not have the ability to determine if the fragments taught by Pawson *et al* are indeed immunogenic, in the absence of evidence to the contrary, the fragments are immunogenic fragments. Further, because the sequence taught by Pawson *et al* is 98.9% identical to SEQ ID No: 2 it necessarily fulfills the limitation of at least 95% identical to that of SEQ ID No: 2. Moreover, Pawson *et al* also disclose fragments that are at least 20 contiguous amino acids from SEQ ID No: 2* (see col. 7, line 41) and therefore falls within the scope of both "no more than two" or "no more than one" single amino acid substitution, deletion, or addition, because no amino acid is either substituted, deleted or added to the fragment. And finally, because SEQ ID No: 2 is 98.9% identical to that of SEQ ID No: 2* and because fragments have been disclosed by Pawson *et al*, it would also "match the aligned sequences" as claimed.

If claim 17 is interpreted as having carriers, Pawson *et al* teaches that pharmaceutical carriers can be included in the invention (see col. 29, lines 23-26).

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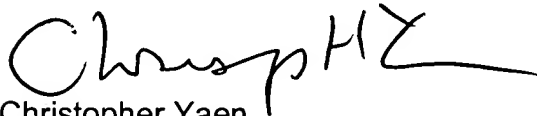
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Chris H Yaen', with a stylized flourish at the end.

Christopher Yaen
Art Unit 1642
January 10, 2005

883-2.rag

Exhibit A

QY 720 VIQLVGMLRGIAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPT 779
 Db 721 VIQLVGMLRGIAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPT 780
 QY 780 YTSALGGKIPIRWTAPEAIQYRKFTSASDVWSYGVIMWEVMSYGERPYWDMTNQDVINAI 839
 Db 781 YTSALGGKIPIRWTAPEAIQYRKFTSASDVWSYGVIMWEVMSYGERPYWDMTNQDVINAI 840
 QY 840 EQDYRLPPPMDCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSG 899
 Db 841 EQDYRLPPPMDCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSG 900
 QY 900 INLPLLDRTIPDYTSFNTVDEWLEAIKMGQYKESFANAGFTSPDVVSQMMEDILRLGVT 959
 Db 901 INLPLLDRTIPDYTSFNTVDEWLEAIKMGQYKESFANAGFTSPDVVSQMMEDILRLGVT 960
 QY 960 LAGHQKKILNSIQVMRAQMNOIQSVEV 986
 Db 961 LAGHQKKILNSIQVMRAQMNOIQSVEV 987

RESULT 6

AAW26366

ID AAW26366 standard; protein; 994 AA.

XX AAW26366;

XX AAW26366;

DT 02-DEC-1997 (first entry)

XX 02-DEC-1997 (first entry)

DE Mouse Nuk tyrosine kinase.

XX Mouse Nuk tyrosine kinase.

KW Nuk tyrosine kinase; Eph receptor tyrosine kinase; signal transduction;

KW axonogenesis; neurodegenerative disease; Alzheimer's disease;

KW Parkinson's disease; Huntington's disease; multiple sclerosis;

KW amyotrophic lateral sclerosis; Wernicke's disease; nerve damage; trauma;

XX ischaemia; stroke.

OS Mus musculus.

XX Mus musculus.

FH Key

FT Peptide

FT Location/Qualifiers

FT 1. .26

FT /label= Sig_peptide

FT 27. .994

FT Protein

FT /label= Mat_protein

FT 27. .548

FT Domain

FT /label= Extracellular_domain

FT 330. .420

FT Region

FT /label= FNIII

FT /note= "fibronectin type III repeat"

FT 444. .534

FT Region

FT /label= FNIII

FT /note= "fibronectin type III repeat"

FT 549. .574

FT Domain

FT /label= Transmembrane_domain

FT 575. .994

FT Domain

FT /label= Cytoplasmic_domain

FT 623. .888

FT Region

FT /label= Tyrosine-kinase_region

XX

PN WO9714966-A1.

XX

PD 24-APR-1997.

XX

PF 10-OCT-1996; 96WO-CA000679.

XX

PR 13-OCT-1995; 95US-0005518P.

XX

PA (MOUN) MOUNT SINAI HOSPITAL CORP.

XX

PI Pawson A, Henkemeyer M;

XX

DR WPI; 1997-245245/22.

DR N-PSDB; AAT84528.

Qy	550	AGAVFLIAVAVIAICNRRGERADSEXTDQLQHYTGSHNTPGKATYIDPFTYEDNEAV	609
Db	558	AGAVFLIAVAVIAICNRRGERADSEXTDQLQHYTGSHNTPGKATYIDPFTYEDNEAV	617
Qy	610	REFAKEIDISCYKIEQVIGAGEFGEVCSGHKLPGKKEIFVAIKTKSGYTEKORDFLS	669
Db	618	REFAKEIDISCYKIEQVIGAGEFGEVCSGHKLPGKKEIFVAIKTKSGYTEKORDFLS	677
Qy	670	EASIMGQDPHNVILHEGVVTKSPVMIITFPMENSGLSDFLRNDGQFVIVLVGMKRG	729
Db	678	EASIMGQDPHNVILHEGVVTKSPVMIITFPMENSGLSDFLRNDGQFVIVLVGMKRG	737
Qy	730	IAAGMKYLLADNNVYHRDLAARILLVNSLVCKVSDPGLSRFLEDSDTPYTSALGKIP	789
Db	738	IAAGMKYLLADNNVYHRDLAARILLVNSLVCKVSDPGLSRFLEDSDTPYTSALGKIP	797
Qy	790	IRKTAPEAIQYKRFTSADSVWSYGIIVMEVWWSYGERPYMTQNDVINALI EODYRLPPM	849
Db	798	IRKTAPEAIQYKRFTSADSVWSYGIIVMEVWWSYGERPYMTQNDVINALI EODYRLPPM	857
Qy	850	DCPSALHQLMLDCWKDRNHRPKFGQIVNTLDRKIRNPNSIKAMAPLSSGINPLDRTI	909
Db	858	DCPSALHQLMLDCWKDRNHRPKFGQIVNTLDRKIRNPNSIKAMAPLSSGINPLDRTI	917
Qy	910	PDTSTNTVDEWLEAIKNGQYKESFANNGFTSPVVSOMMEDILRLGVTLAGHOKKILN	965
Db	918	PDTSTNTVDEWLEAIKNGQYKESFANNGFTSPVVSOMMEDILRLGVTLAGHOKKILN	977
Qy	970	SIQWRAQNMQIQSVEV 986	
Db	978	SIQWRAQNMQIQSVEV 994	
RESULT 7			
AAU01907			
ID	AAU01907	standard; protein; 994 AA.	
AC	AAU01907;		
XX			
XX	29-AUG-2001	(first entry)	
DT			
XX			
DE	Murine neural kinase (Nuk) polypeptide.		
XX			
KW	Neural kinase; Nuk; receptor; tyrosine kinase; axonal migration; stroke;		
KW	nerve fibre; cell-cell interaction; axonogenesis; neuronal development;		
KW	regeneration; neurodegenerative disorder; Alzheimer's disease; ischaemia;		
KW	Parkinson's disease; Huntington's disease; demyelinating disease;		
KW	multiple sclerosis; amyotrophic lateral sclerosis; deficiency disease;		
KW	Wernicke's disease; nutritional polyneuropathy; multistem degeneration;		
KW	progressive supranuclear palsy; Shy Drager's syndrome; mouse;		
KW	olivoponto cerebellar atrophy; peripheral nerve damage.		
XX			
OS	Mus musculue.		
XX			
XX			
FT	Key	Location/Qualifiers	
FT	Peptide	1..26	
FT		/note="Signal peptide"	
FT	Domain	26..548	
FT		/note="extracellular domain, preferably residues 26-544"	
FT	Protein	27..994	
FT		/note="nature murine neural kinase"	
FT	Domain	52..119	
FT		/note="Ig-like domain"	
FT	Region	239..268	
FT		/note="Ig-like Nuk repeat"	
FT	Region	330..420	
FT		/note="Fibronectin type III repeat"	
FT	Region	444..534	
FT		/note="Fibronectin type III repeat"	
FT	Domain	549..574	
FT		/note="hydrophobic transmembrane domain"	
FT	Binding-site	600..618	
FT		/note="SH2 domain binding site"	

W

STATE: Ontario
COUNTRY: Canada
ZIP: M5H 3Y2
COMPUTER READABLE FORM:
MEDIUM TYPE: Floppy disk
COMPUTER: IBM PC compatible
OPERATING SYSTEM: PC-DOS/MS-DOS
SOFTWARE: Patentin Release #1.0, Version #1.25
CURRENT APPLICATION DATA:
APPLICATION NUMBER: US/06/542,635
FILING DATE:
CLASSIFICATION: 800
ATTORNEY/AGENT INFORMATION:
NAME: McElmuid, Shona S.
REGISTRATION NUMBER: 38,798
REFERENCE/DOCKET NUMBER: 3153-162
TELECOMMUNICATION INFORMATION:
TELEPHONE: (416) 364-7311
TELEFAX: (416) 361-1398
TELEX: 06-23115
INFORMATION FOR SEQ ID NO: 2:
SEQUENCE CHARACTERISTICS:
LENGTH: 994 amino acids
TYPE: amino acid
STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: protein
ORIGINAL SOURCE:
ORGANISM: Mus musculus
DEVELOPMENTAL STAGE: Embryo
IMMEDIATE SOURCE:
LIBRARY: Ianda gct10 cDNA library
CLONE: Combined pMURACE A2 and K2 and cDNA clones
POSITION IN GENOME:
CHROMOSOME/SEGMENT: Distal end of chromosome 4
MAP POSITION: near the abd-1 mutation
US-08-542-635-2

```
Query Match      98.9%; Score 5130; DB 3; Length 994;
Best Local Similarity 99.5%; Pred. No. 0;
Matches 972; Conservative 4; Mismatches 1; Indels 0; Gaps 0;
```

Qy	10	ILLLPLLAVEETLMDSTTAAELGMAVHPSPGSEVSGIDENMTIRYQVCNFESSQ	69
Db	18	ILLLPLLAABEETLMDSTTAAELGMAVHPSPGSEVSGIDENMTIRYQVCNFESSQ	77
Qy	70	NNMLAKTFLRRGARHIVENKFSVRDCCSIPTSPVSCBETNLVYEADPDQATKTFPN	129
Db	78	NNMLAKTFLRRGARHIVENKFSVRDCCSIPTSPVSCBETNLVYEADPDQATKTFPN	137
Qy	130	MMENPMVKYDTLADDESFOVDLGRVVKINTEVNSFGPVNSGFLYLAPODYGCMSLYLA	189
Db	138	MMENPMVKYDTLADDESFOVDLGRVVKINTEVNSFGPVNSGFLYLAPODYGCMSLYLA	197
Qy	190	VRVFYKRCRIIONGAIPOETLSGAEISTLYAARGCIANAEVDVPFKLYCNGDGEMLV	249
Db	198	VRVFYKRCRIIONGAIPOETLSGAEISTLYAARGCIANAEVDVPFKLYCNGDGEMLV	257
Qy	250	PIGRCKAGAEAVENGTVCRGCPSGTFXANOGDEACTHCPIINSRTTSEGLTNCVCNGY	309
Db	258	PIGRCKAGAEAVENGTVCRGCPSGTFXANOGDEACTHCPIINSRTTSEGLTNCVCNGY	317
Qy	310	YRADLDPELDMCTTIPAPQAVISSVNETSLMLWTPRDSCGREDLVYNIICKSCGSGR	369
Db	318	YRADLDPELDMCTTIPAPQAVISSVNETSLMLWTPRDSCGREDLVYNIICKSCGSGR	377
Qy	370	GACTRCGDNVYAPRQGLTEPRITYSDLLATTOYTFEIOAVNGVTQSPSPQFASVNI	429
Db	378	GACTRCGDNVYAPRQGLTEPRITYSDLLATTOYTFEIOAVNGVTQSPSPQFASVNI	437
Qy	430	TTNQAAPSAVSIMHVSRTVDSITLWSQPDQPNGVILDYELAYEKELESEYNAIAIKSP	489
Db	438	TTNQAAPSAVSIMHVSRTVDSITLWSQPDQPNGVILDYELAYEKELESEYNAIAIKSP	497

Exhibit B (cont.)

Mon Aug 30 08:48:58 2004

us-09-914-88

Qy 490 TMTVTVOGLKAGAIYVFOVRARTVAGYGRYSGKMYFQTMTEABYQTSIQEKLPLIIGSSA 549
Db 498 TMTVTVOGLKAGAIYVFOVRARTVAGYGRYSGKMYFQTMTEABYQTSIQEKLPLIIGSSA 557
Qy 550 AGLVFLIAVVVIAIVCNRRGFERADSEYTDKLOHYTSGHMTPGMKIYIDPFTYEDPNEAV 609
Db 558 AGLVFLIAVVVIAIVCNRRGFERADSEYTDKLOHYTSGHMTPGMKIYIDPFTYEDPNEAV 617
Qy 610 REFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLPKREIFVAIKTLKSGYTEKQRRDPLS 669
Db 618 REFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLPKREIFVAIKTLKSGYTEKQRRDPLS 677
Qy 670 EASIMGQFDHPNVHLEGVVTKSTPVMIIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRG 729
Db 678 EASIMGQFDHPNVHLEGVVTKSTPVMIIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRG 737
Qy 730 IAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDPGLSRFLEDDTSDPTYTSALGGKIP 789
Db 738 IAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDPGLSRFLEDDTSDPTYTSALGGKIP 797
Qy 790 IRWTAPEAIQYRKFTSASDVMSYGIWMVEVMSYGERPYWDMTNQDVINAIEQDYRLPPPM 849
Db 798 IRWTAPEAIQYRKFTSASDVMSYGIWMVEVMSYGERPYWDMTNQDVINAIEQDYRLPPPM 857
Qy 850 DCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMI RNPNLSLKAMAPLSSGINLPLLDRTI 909
Db 858 DCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMI RNPNLSLKAMAPLSSGINLPLLDRTI 917
Qy 910 PDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMEDILRLGVTLAGHOKKILN 969
Db 918 PDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMEDILRLGVTLAGHOKKILN 977
Qy 970 SIQVMRAQMNIQSVEV 986
Db 978 SIQVMRAQMNIQSVEV 994